Physiologically-Based Pharmacokinetic (PB-PK) Modeling For Dermal Absorption Of Pesticides (Malathion) In Man

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HS-1678

March 26, 1993; Revised June 17, 1996

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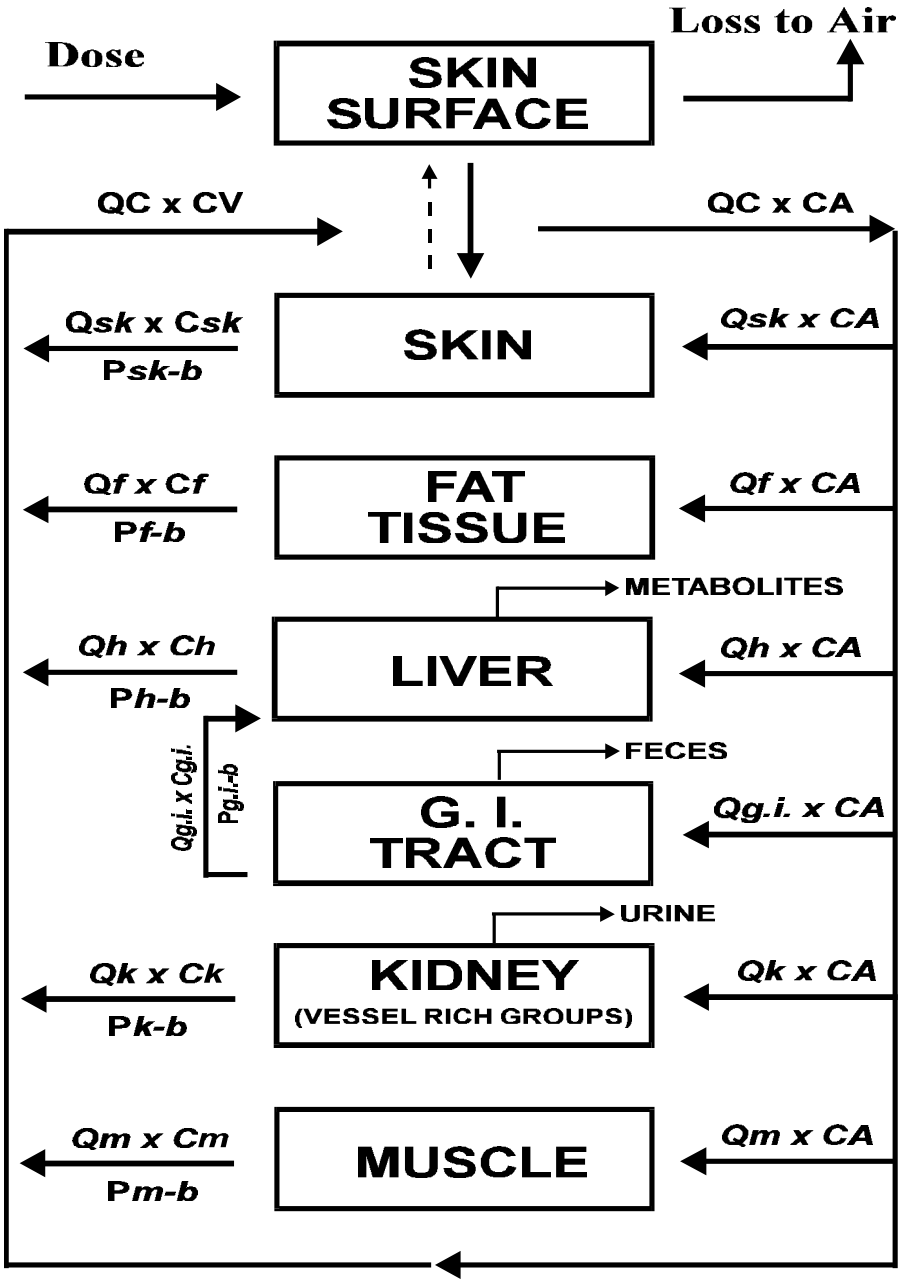
32nd Society of Toxicology Annual Meeting, Poster Number 1386
March 14-18, 1993, New Orleans, Louisiana

ABSTRACT

Measurement of pesticide penetration through the human skin is an essential step for an adequate scientific assessment of health risk involved in agricultural activities. This presentation discusses the effectiveness of PB-PK modeling as a computer simulation technique in quantifying the skin permeability of pesticides. Basic to this simulation technique is the application of a mathematical model composed of several pre-selected anatomical compartments which include the skin as the only route of exposure. Each of these compartments has its own characteristic blood flow, volume, tissue-blood partition coefficient, and metabolic constant(s) that together are deemed responsible for the chemical's disposition in that region. In this presentation, the sum of the total predicted metabolism, tissue storage, and excretion of malathion was used as a measure of the total amount absorbed. The data used to drive the model predictions were the serial, cumulative urinary excretions of malathion acid metabolites collected in an in-house human metabolism study*. The excretions were collected after a single dose of 3.0 or 8.5 μmoles malathion per cm^2 was applied to the adult male forearms for 10 or 12 hours. A comparison was made between malathion absorption simulated in this study (2 - 3% of the applied high dose) and those calculated from comparable human literature data (~ 4%). The results from this comparison indicated that PB-PK modeling can be an effective alternative to the classic, *in vivo* analysis of pesticide dermal absorption in man.

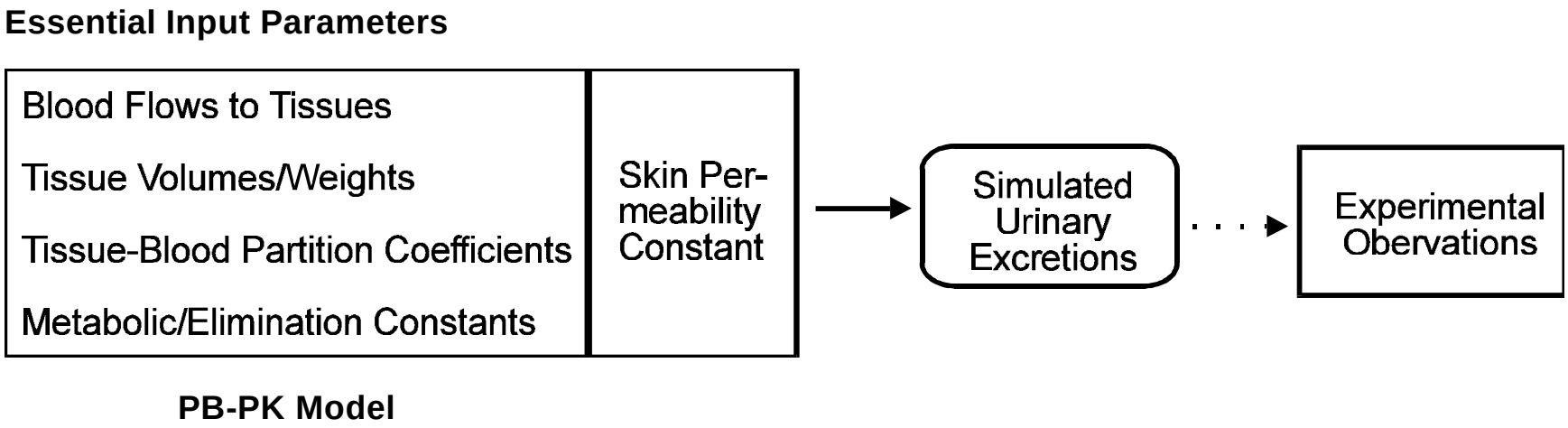
***conducted in 1989 by Dr. Robert Krieger, formerly chief of the Worker Health and Safety Branch.**



(Q*i* = blood flow to tissue *i*; P*i-b* = tissue *i* - blood partition coefficient; C*i* = concentration in tissue *i*; QC = cardiac output; CV = mixed venous concentration; CA = mixed arterial concentration; and CA = CV)

Figure 1. A typical physiologically-based pharmacokinetic (PB-PK) model for dermal exposure. [Reproduced from Dong *et al.* (1994) with permission copyright American Chemical Society]

Research Questions: ***What Should Be the Skin Permeability Constant in the Model If the Simulated Urinary Excretions Were Set Consistent with Its Experimental Observations*?***



*(*While Other Parameters Were Being Held Constant)*

FIGURE 2. ANALYTICAL SCHEME FOR SIMULATION OF SKIN PERMEABILITY CONSTANT

Equations Typically Used in a PB-PK Model for Dermal Exposure[a]

$$CA = \{(Q_{sk} \times C_{sk}/P_{sk\text{-}b}) + (Q_f \times C_f/P_{f\text{-}b}) + (Q_h \times C_h/P_{h\text{-}b}) + (Q_k \times C_k/P_{k\text{-}b}) + (Q_m \times C_m/P_{m\text{-}b})\}/QC. \quad (1)$$

Mixed arterial (CA) concentration is the sum of the amounts eliminated in the individual compartments divided by the cardiac output QC (*i.e.*, by the sum of the individual Q_i). The amount eliminated in each compartment *i* is denoted by $Q_i \times C_i / P_{i\text{-}b}$, where Q_i = blood flow to tissue *i*, C_i = concentration in tissue *i*, and $P_{i\text{-}b}$ = tissue *i*/blood partition coefficient. (Throughout this table, the following notations are used: sk = skin; f = fat; h = hepatic; k = kidney; g.i. = GI tract; m = muscle; surf = skin surface; met = metabolite; u = urine; fec = feces; and AMT = amount.)

$$dAMT_{surf}/dt = K_{sp} \times A \times (C_{sk}/P_{sk\text{-}a} - C_{exp}) - K_a \times AMT_{surf}. \quad (2)$$

The amount *on* the skin (AMT_{surf}) changes over time as a function of three events: (1) the amount diffused from *inside* to *outside* of the skin *(although at times this amount is negligible)*; (2) the amount absorbed *into* the skin; and *c*) the amount lost to the air. (K_{sp} = skin permeability constant; A = surface area exposed; $P_{sk\text{-}a}$ = skin-air partition coefficient; K_a = evaporation constant; and C_{exp} = concentration of dose applied *topically*.) [Where C_{exp} is averaged *air* concentration, both this and Eq. (3) will no longer be applicable since in that case the applied dose will not diminish over time.]

$$dAMT_{air}/dt = K_a \times AMT_{surf}. \quad (3)$$

The amount lost to the air is a function of $K_a \times AMT_{surf}$.

$$dAMT_{sk}/dt = K_{sp} \times A \times (C_{exp} - C_{sk}/P_{sk\text{-}a}) + Q_{sk} \times (CA - C_{sk}/P_{sk\text{-}b}). \quad (4)$$

The amount absorbed into the skin is a function of three events: (1) the amount diffused *into* the skin; (2) the amount diffused from *inside* to *outside* of the skin; and (3) the amount of difference between that perfused to and that eliminated in the skin tissue.

$$dAMT_f/dt = Q_f \times (CA - C_f/P_{f\text{-}b}). \quad (5)$$

The amount in fat is related directly to the amount of difference between that perfused to and that eliminated in the fat tissue.

$$dAMT_{met}/dt = \{V_{max} \times C_h)\}/\{(K_m \times P_{h\text{-}b}) + C_h\} \quad (6)$$

This metabolism rate is based on the well-known Michaelis-Menten equation; for some chemicals this equation may occur in a tissue organ other than the hepatic system or may take another form, such as a first-order reaction.

$$dAMT_h/dt = Q_h \times (CA - C_h/P_{h\text{-}b}) + (Q_{g.i.} \times C_{g.i.}/P_{g.i.\text{-}b}) - dAMT_{met}/dt. \quad (7)$$

$$dAMT_u/dt = K_u \times AMT_k \quad (K_u = \text{urinary constant}). \quad (8)$$

$$dAMT_k/dt = Q_k \times (CA - C_k/P_{k\text{-}b}) - K_u \times AMT_k. \quad (9)$$

$$dAMT_{g.i.}/dt = Q_{g.i.} \times (CA - C_{g.i.}/P_{g.i.\text{-}b}) - K_{fec} \times GI \quad (K_{fec} = \text{fecal constant}). \quad (10)$$

$$dAMT_{fec}/dt = K_{fec} \times GI. \quad (11)$$

$$dAMT_m/dt = Q_m \times (CA - C_m/P_{m\text{-}b}). \quad (12)$$

[a] These equations are summarized graphically in Figure 1. Equations (7) through (12) are not elaborated here because upon reviewing the first few equations, the reader should find their interpretations all to be repetitive. For dermal exposure, mixed venous concentration (as denoted by CV in Figure 1) is assumed to be approximately equal to CA.

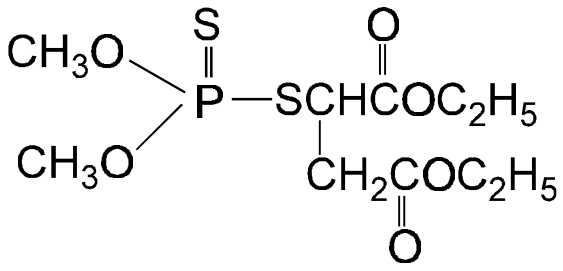
EXTENSION OF FICK'S *SECOND* LAW OF DIFFUSION

$$K_{SP} = \frac{ABS}{A \times \Delta C \times t}$$

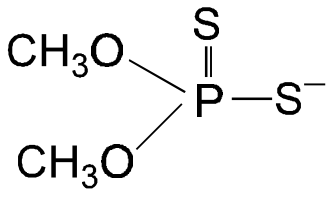
(The Amount Absorbed, *ABS*, from Dermal Exposure [of Skin Area *A* at Concentration Gradient ΔC for *t* Hours] Is Directly Proportional to the Pesticide's Skin Permeability, K_{SP}.)

% Dermal Absorption ≡ (*ABS*/Applied Dose) x 100

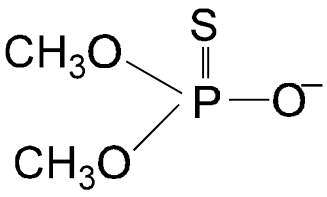
≈ (*ABS*/ΔC x *A*) x 100 = (K_{SP} x *t*) x 100



Malathion



DMDTP



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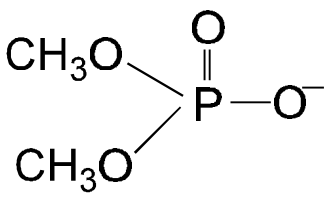

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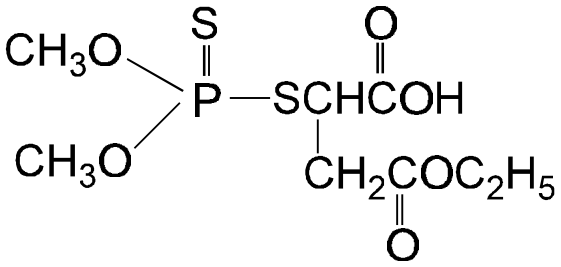
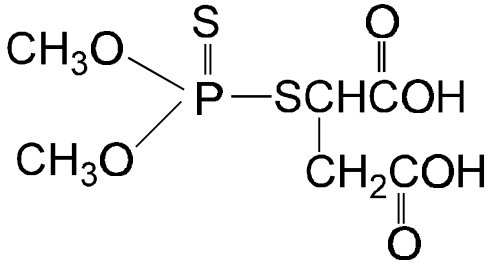
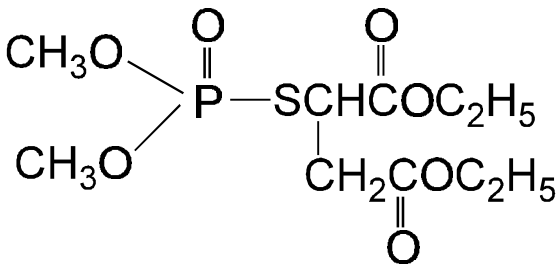


Mono-Acid



Di-Acid



Malaoxon

Input Parameters Used for Modeling Dermal Absorption of Malathion[a,b,c]

BW = 150	**Body weight of human volunteer (kg)**
QC = 10.79	**Cardiac output (L/min)**
QF = 0.33	**Blood flow to fat (L/min)**
QGI = 1.99	**Blood flow to G. I. tract (L/min)**
QK = 3.74	**Blood flow to kidney (L/min)**
QH = 2.49	**Blood flow to liver (L/min)**
QM = 1.99	**Blood flow to muscle (L/min)**
QSK = 0.25	**Blood flow to skin (L/min)**
PFC = 0.143	**Percentage Fat**
PGIC = 0.034	**Percentage G.I. tract**
PKC = 0.039	**Percentage kidney**
PHC = 0.021	**Percentage liver**
PMC = 0.429	**Percentage muscle**
PSKC = 0.039	**Percentage skin**
P_{F-b} = 775.5	**Fat/blood partition coefficient**
P_{GI-b} = 15.0	**G.I. Tract/blood partition coefficient**
P_{K-b} = 17.0	**Kidney/blood partition coefficient**
P_{H-b} = 33.6	**Liver/blood partition coefficient**
P_{M-b} = 22.8	**Muscle/blood partition coefficient**
P_{SK-b} = 25.0	**Skin/blood partition coefficient**
V_{max} = 4.89 x 10^{-4}	**Michaelis-Menten rate (moles/min)**
K_m = 1.35 x 10^{-4}	**Michaelis-Menten concentration (*M*)**
K_{sp} = 1.5 - 50 x 10^{-5}	**Skin permeability constant (min^{-1})**
K_a = 2.0 x 10^{-4}	**Evaporation constant (min^{-1})**
K_u = 25	**Urinary constant (min^{-1})**
K_f = 0.1	**Fecal constant (min^{-1})**

***a*incorporated into a BASICA program written by first author (Dong, 1994).**

***b*adopted from Cal/EPA Office of Environmental Health Hazard Assessment (1991) and the work by Rabovsky and Brown (1993).**

***c*blood flows to various tissues were scaled up for body weight difference between volunteer and standard man (BW_1 = 70 kg) using the correction factor $(BW_2/BW_1)^{2/3}$, as common practice.**

Fig 3A. Simulation of Human Urinary Excretion of Malathion with Skin Permeability Set at 3.7 x 10^{-5}/min and Delay Time at 8.5 hr for Absorption/Disposition

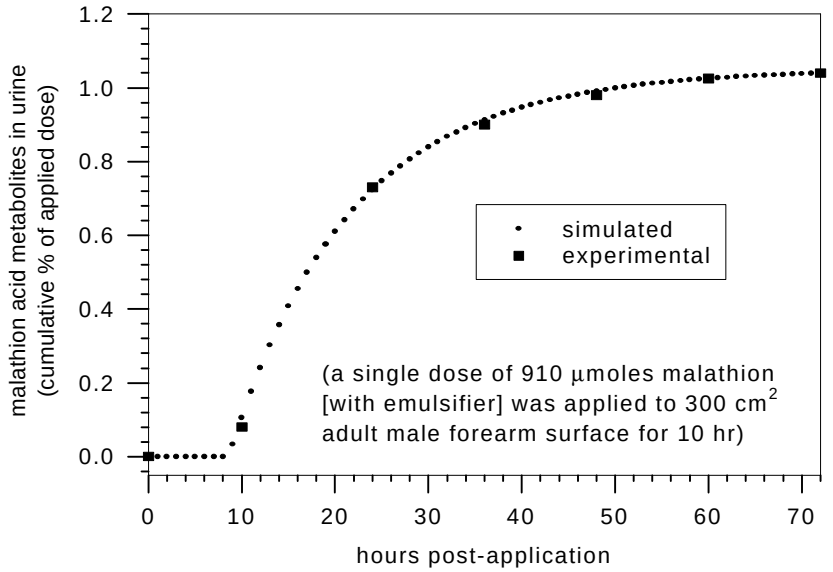


Fig 3B. Correlation of Experimental Urinary Excretions with Those Simulated Using a Skin Permeability of 3.7 x 10^{-5}/min and an 8.5 hr Delay for Absorption/Disposition

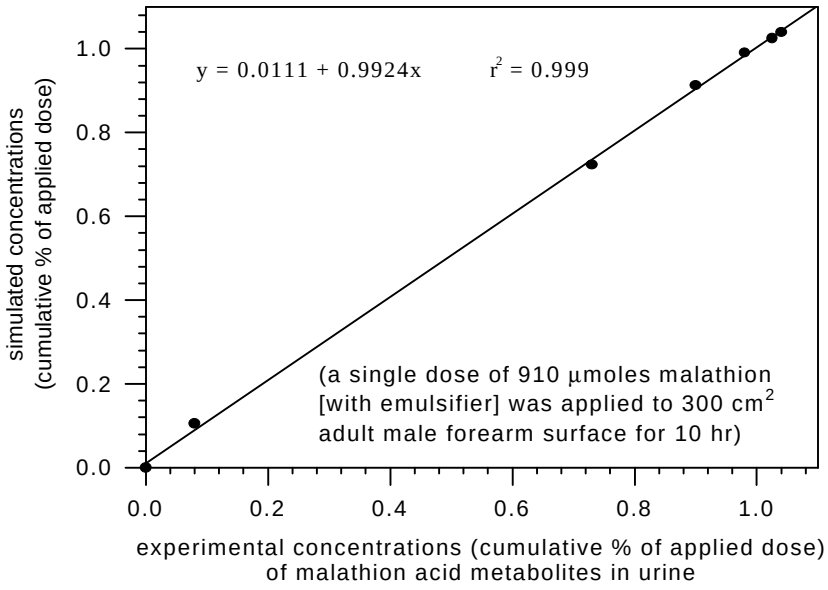


Fig 4A. Simulation of Human Urinary Excretion of Malathion with Skin Permeability Set at 2.82 x 10^{-5}/min and Delay Time at 10.5 hr for Absorption/Disposition

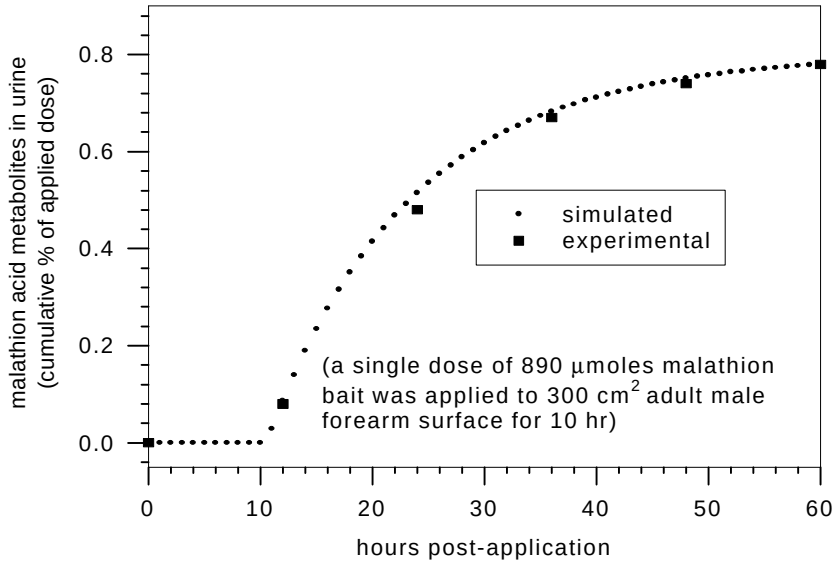


Fig 4B. Correlation of Experimental Urinary Excretions with Those Simulated Using a Skin Permeability of 2.82 x 10^{-5}/min and a 10.5 hr Delay for Absorption/Disposition

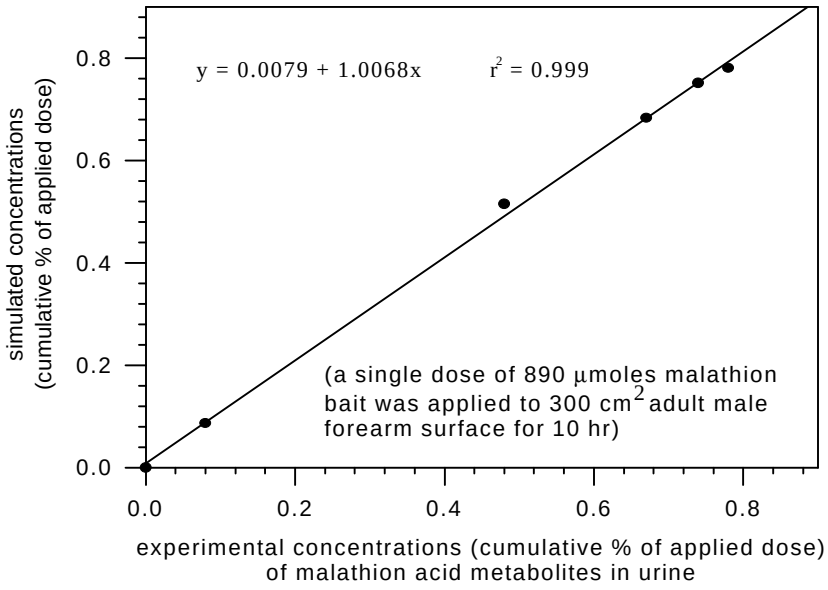


Fig 5A. Simulation of Human Urinary Excretion of Malathion with Skin Permeability Set at 4.3 x 10^{-5}/min and Delay Time at 6.5 hr for Absorption/Disposition

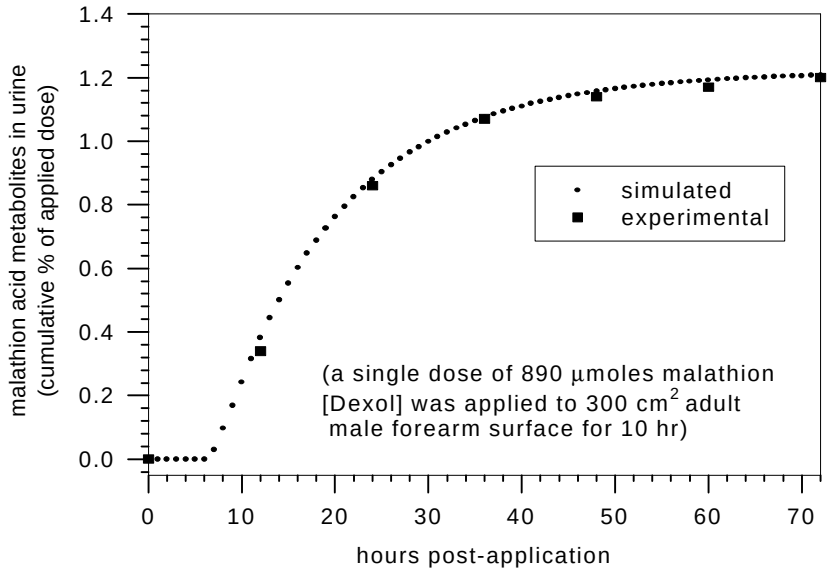


Fig 5B. Correlation of Experimental Urinary Excretions with Those Simulated Using a Skin Permeability of 4.3 x 10^{-5}/min and a 6.5 hr Delay for Absorption/Disposition

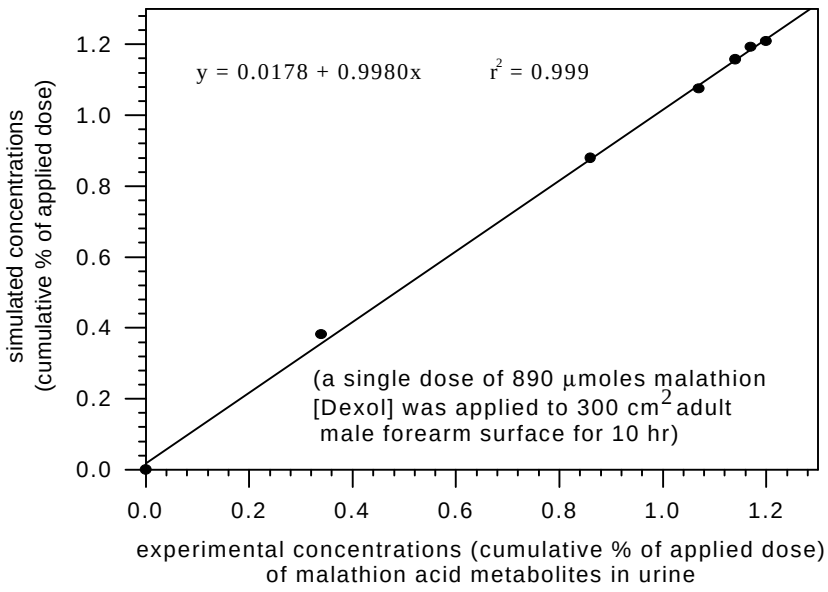


Fig 6A. Simulation of Human Urinary Excretion of Malathion with Skin Permeability Set at 2.6 x 10^{-5}/min and Delay Time at 4.0 hr for Absorption/Disposition

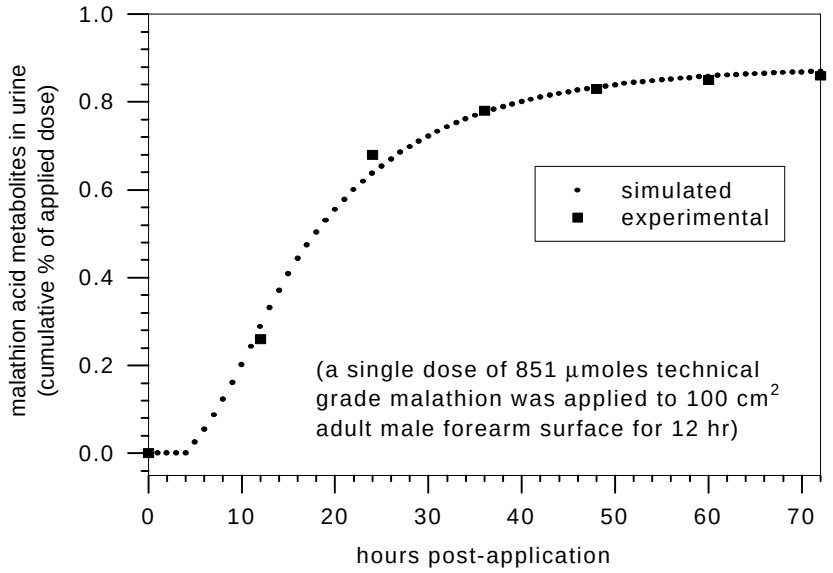
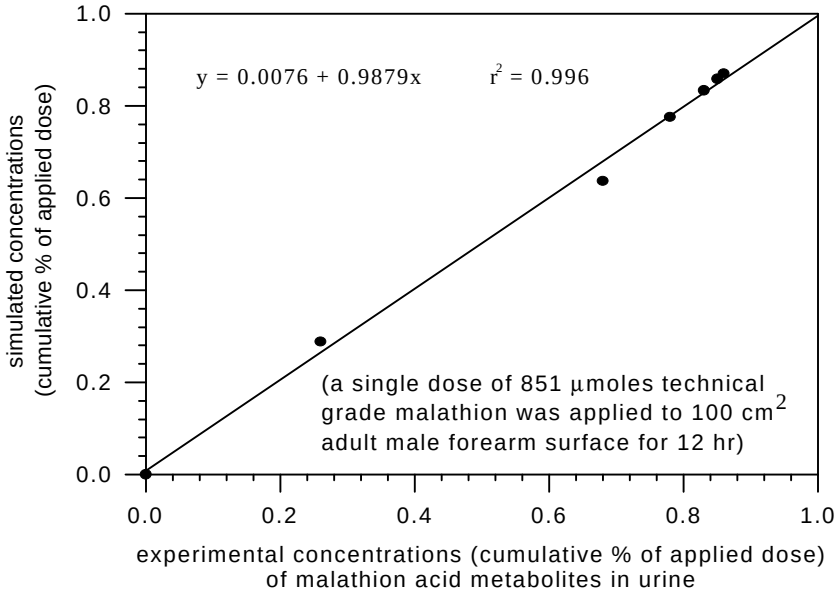


Fig 6B. Correlation of Experimental Urinary Excretions with Those Simulated Using a Skin Permeability of 2.6 x 10^{-5}/min and a 4.0 hr Delay for Absorption/Disposition



CONCLUSIONS

1. **The serial, cumulative urinary excretions simulated in the four models, each taking a specific malathion skin permeability, were seen to correlate extremely well with those observed experimentally (Figs. 3 through 6). These results supported the presumption that PB-PK modeling can be an effective and efficient alternative to the *classic, in vivo* analysis of pesticide dermal absorption.**

2. **Using the skin permeability specified in the four models (Figs. 3 through 6), malathion absorption for a 10- or 12-hour exposure was calculated to be between 1.7% and 2.6% of the initial applied dose (*see* bottom of p. 6 for calculation equation). The time lapse between first dermal contact and metabolism first took place was estimated to be between 4 to 10.5 hours.**

3. **These calculated absorption rates (1.7% - 2.6%) were found highly comparable with those provided in a literature review (Fong *et al.* 1990), in which a 4.0% dermal absorption was concluded for workers with similar day-long exposure following a single *high* dose (in *mg*/cm^2) of malathion. That review covered all available *in vivo* studies at the time, including the work by Feldmann and Maibach (1974), Hayes *et al.* (1960), and Wester *et al.* (1983).**

Note: The graphics and simulation results provided here are slightly different from those presented in the original poster paper, due to use of improved simulation program (Dong, 1994) and scientific graphing software that now runs in Microsoft Windows â. The software used earlier for graphing runs on a Macintosh only, a type of computer that has now become obsolete to this Branch.

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